REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims

Pending claims

Claims 31 to 42 and 53 to 97 are pending (claims 1 to 30 and 43 to 52 have been canceled).

Claims added in the instant amendment

Claims 98 through 107 are added in this amendment. Thus, after entry of the instant amendment, claims 31 to 42 and 53 to 106 will be pending and under examination.

Outstanding Rejections

Claims 31 to 42 and 53 to 97 are rejected under 35 U.S.C. §112, second paragraph. Claims 31 to 42 and 53 to 97 are rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for claims wherein the modifications are introduced by synthetic gene reassembly can be found, inter alia, on page 13, lines 14 to 30. Applicants submit that no new matter is introduced by the present amendments.

Claim objections

Applicants thank the Examiner for noting the inadvertent error in the listing of claims in their response of July 31, 2003; claims 32 to 42 are pending and are included in the instant listing of claims.

Objections were made to the language of claims 31, 53, 65 and 77. The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, second paragraph

Claims 31 to 42 and 53 to 97 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard and the invention.

The Office alleges that Applicants' amendment to claims 31, 53, 65, and 77, regarding addition of a selection step in which a generated nucleic acid variant is tested or screened to determine if it encodes a polypeptide having a polymerase activity, is confusing. The instant amendment addresses this issue.

The Office alleges claim 91 is indefinite. The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Written Description

The rejection against claims 65 to 88, was maintained, and claims 89 to 97 were newly rejected, under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants thank the Examiner for withdrawing the 35 U.S.C. §112, first paragraph, written description rejection against claims 31 to 42.

However, the Patent Office remained concerned (and hence has maintained the rejection of claims 65 to 76 and 77 to 88, and has newly rejected claims 89 to 97) about the number of representative species encompassed by the claimed genus of nucleic acids used in the claimed methods. In particular, the invention of claims 65 to 76, 77 to 88 and 89 to 97 comprises the step of obtaining a nucleic acid comprising a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO:1 and encoding a polypeptide having a polymerase activity, or its complement.

To address the Patent Office's concerns, Applicants submit for consideration a Rule 132 expert declaration by co-inventor Dr. Walter Callen, who was an expert in the field of

molecular biology and enzyme development at the time of the invention. Dr. Callen declares that assays for identifying nucleic acids that encode polypeptides having polymerase activity were conventional and routine in the art at the time of the invention. Dr. Callen declares that procedures for identifying polypeptides having polymerase activity, including thermotolerant or thermostable polymerase activity and phytase activity under varying conditions, such as varying temperature and pH conditions, were conventional and routine in the art at the time of the invention. Dr. Callen declares that making polypeptide-encoding nucleic acids of different sizes or varying sequences based on an exemplary sequence, and screening them for polymerase activity under various conditions was a predictable art at the time of the invention. Accordingly, one of ordinary skill in the art using the teaching of the specification would have been able to ascertain what polymerase-encoding nucleic acids, including nucleic acids of varying sizes and sequences, were within the scope of the claims with reasonable clarity to recognize that Applicants' were in possession of the invention at the time of filing.

Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that the amended claims are sufficiently described in the specification to overcome the 35 U.S.C. §112, first paragraph, written description rejection.

Enablement

The rejection against claims 31 to 42 and 65 to 88, was maintained, and claims 89 to 97 were newly rejected, under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Patent Office notes that the specification is enabling for a method of generating a polymerase variant comprising obtaining a nucleic acid comprising SEQ ID NO:1 and sequences complementary thereto, and modifying, deleting or adding one or more nucleotides in said sequence, wherein the variant maintains polymerase activity.

However, it is alleged that the specification does not reasonably provide enablement for the extremely large number of methods broadly encompassed by the claims,

including all methods of generating variant polynucleotides using a nucleic acid of the invention. To address the Patent Office's concerns Applicants submit for consideration a Rule 132 expert declaration by co-inventor Dr. Walter Callen. Dr. Callen declares that procedures for modifying nucleic acids were conventional and routine in the art at the time of the invention. Dr. Callen declares that one of ordinary skill in the art using the teaching of the specification would have been able to select any known method of modifying nucleic acids, including any one or a combination of exemplary methods set forth in the specification, including error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, in vivo mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, ligation reassembly or gene site saturated mutagenesis (GSSM™), to make a variant of SEQ ID NO:1, or a variant of a nucleic acid having 70% sequence identity to SEQ ID NO:1, or a variant of a nucleic acid comprising a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO:1, to practice the methods of the invention without undue experimentation.

The Patent Office also expressed concerns that the disclosure does not provide sufficient guidance beyond the exemplary SEQ ID NO:1 as to how one would obtain and then modify this sequence such that polymerase-encoding variants would be generated. It is alleged that it is not routine in the art to screen for multiple substitutions or modifications to generate a polymerase with a reasonable expectation of success.

To address these concerns, in the attached Rule 132 expert declaration, Dr. Callen declares that methods for changing, or varying, nucleic acids sequences were well known in the art at the time of the invention. Dr. Callen declares that it was considered routine by one skilled in the art at the time of the invention to screen for multiple substitutions or multiple modifications in a nucleic acid sequence for functional variations, e.g., variant nucleic acids that encode a polymerase enzyme. For example, high through-put methods for screening for polymerase activity, such as polymerase chain reaction (PCR), were well known in the art. Dr. Callen declares that while the numbers of samples needed to be screened may have been high, the screening procedures were routine and successful results (e.g., finding variant nucleic acids encoding polymerases, such as thermostable polymerases) predictable. Accordingly, Dr. Callen declares that at the time of the invention it would have been considered routine by one skilled in

the art to generate and screen multiple substitutions or multiple modifications in a nucleic acid sequence and predictably generate functional variants.

The Patent Office is also concerned that the specification does not support the broad scope of the claims which encompass all methods of modifying a nucleic acid of the invention, including a fragment of at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO:1, because, inter alia, the specification does not describe regions of protein structure which may be modified without affecting function or activity.

To address these concerns, in the attached Rule 132 expert declaration Dr. Callen declares that it was not necessary for the skilled artisan to understand which specific regions of polymerase structure may be modified without affecting function or activity, or, which specific regions of polymerase structure should be modified to generate altered enzyme activity, to practice the methods of the invention because methods for modifying sequences, generating polymerase-encoding sequences and screening for activity at the time of the invention were routine and predictable. For example, Dr. Callen declares that methods for sequence modifications were sufficiently routine and predictable at the time of the invention to predictably generate polymerase encoding sequences without need of knowing which specific regions of polymerase structure affect polymerase function or activity. For example, on pages 32 to 35, the specification gives a detailed description of an exemplary method for sequence modification called Gene Site Saturation Mutagenesis™ (GSSM™). Dr. Callen declares that in one aspect of GSSM™, degenerate oligonucleotides comprising degenerate N,N,N cassettes can be used for subjecting each original codon in a parental polynucleotide template to a full range of codon substitutions. Thus, GSSM™ allows for mutagenizing each and every amino acid position in a parental polypeptide to generate amino acid changes that can be routinely screening for their effect on activity. Dr. Callen declares that methods for modifying nucleic acid sequences such as GSSM™ known at the time of the invention made methods that require previous knowledge of protein tertiary structure, active sites and the like obsolete and unnecessary. Accordingly, Dr. Callen declares that using methods known in the art at the time of the invention, e.g., GSSM™, it would not have been necessary to understand which specific regions of polymerase structure can be modified to generate variant enzymes to practice the methods of the invention.

The Patent Office is also concerned that the specification does not provide sufficient guidance to one of ordinary skill in the art as to which variant nucleic acid falls within the scope of the claimed method. However, as discussed above, and declared by Dr. Callen, methods for determining the requisite structure (sequence based on percent sequence identity to an exemplary nucleic acid) and function (polymerase activity) are clearly set forth in the specification. For example, by 1996, high through-put *in vivo* (e.g., whole cell) nucleic acid expression and polymerase activity screening protocols were well known in the art. In particular, high through-put methods to screen for polymerase activity, such as polymerase chain reaction (PCR), were well known in the art. The specification sets forth an exemplary polymerase screening assay to determine if a nucleic acid is within the scope of the claimed methods, inter alia, on pages 69 to 70, Example 1. Methods for determining sequence identity were also routine and well known in the art at the time of the invention. The specification describes methods for determining whether a nucleic acid has a percent sequence identity to an exemplary polynucleotide on, inter alia, pages 55 to 69 of the specification. As declared by Dr. Callen, all of these protocols were routine in the art at the time of the invention and positive results (e.g., determining if a nucleic acid is within the scope of the claimed methods, e.g., a nucleic acid at least 30 consecutive nucleotides of a sequence having at least 70% identity to the sequence set forth in SEQ ID NO:1) predictable. As, as discussed previously, while the numbers of alternative species that need to be screened may be high, the protocols for screening were routine and positive results predictable. Accordingly, the specification provides sufficient guidance to one of ordinary skill in the art to make and use the described genus of nucleic acid to practice the claimed methods.

Applicants respectfully submit that the pending claims meet the enablement requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that the specification sufficiently described how to make and use the claimed methods to satisfy the requirements of 35 U.S.C. §112, first paragraph.

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CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Respectfully submitted,

Date: April 21, 2004

Gregory P. Einhorn
Reg. No. 38,440

Morrison & Foerster LLP
3811 Valley Centre Drive, Suite 500
San Diego CA 92130
direct dial 858 720 5133
fax 858 720 5125